# Effects of Recombinant Activated Factor VII in Traumatic Nonsurgical Intracranial Hemorrhage

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**OBJECTIVE:** To determine whether treatment with recombinant activated factor VII (rFVIIa) will prevent progression of bleeding in nonsurgical hemorrhagic traumatic brain injury (TBI).

**METHODS:** Chart review from the trauma registry of a level 1 trauma center between January 1, 2002 and December 31, 2004 identified 2 patients who received rFVIIa for progressive hemorrhagic TBI. These patients were given a single dose of rFVIIa (120 mcg/kg) after a repeat head computed tomography (CT) scan showed worsening of intracranial bleeding. Pre-rFVIIa and post-rFVIIa coagulation parameters and postintervention CT scans were performed. A matched convenience sample was drawn from the institution's trauma registry reflecting similar injury patterns.

**RESULTS:** The 2 patients who received rFVIIa were ages 61 and 79 years; the patients in the matched convenience sample were 57 and 63 years. Both sets of patients comprised 1 man and 1 woman who had suffered blunt trauma, including hemorrhagic TBI, and were matched according to age, gender, and injury severity score (ISS). During their hospital course, repeat CT scans documented worsening of intracranial hemorrhage in both cohorts. In the rFVIIa patients, follow-up CT showed overall improvement of head injury compared with the convenience sample. The rFVIIa patients also saw an appreciable decrease in both prothrombin time (PT) and international normalized ratio (INR).

**CONCLUSIONS:** In hemorrhagic TBI, rFVIIa has the potential to limit or even halt the progression of bleeding that would otherwise place growing pressure on the brain. A prospective, randomized multicenter trial is planned to elucidate this hypothesis. (Curr Surg 63:310-317. © 2006 by the Association of Program Directors in Surgery.)

**KEY WORDS:** traumatic brain injury, coagulopathy, hemorrhage, recombinant factor VIIa, thromboembolism

## INTRODUCTION

Recombinant activated factor VII (rFVIIa; NovoSeven; Novo Nordisk Pharmaceuticals, Inc. Princeton, New Jersey) was originally developed to treat patients with hemophilia who had developed inhibitors to either factor VIII or factor IX. Its mechanism of action suggests that its hemostatic enhancing effects are limited to the site of injury and that systemic thrombosis due to activation of the coagulation cascade does not occur.[1,2] These properties make rFVIIa ideal for different populations with severe hemorrhage. The literature now contains multiple case reports and retrospective data that suggest that rFVIIa is safe and efficacious for treatment of exsanguinating hemorrhage in the trauma patient. Prospective clinical trials are already underway to support this conclusion. However, there is a paucity of data regarding the role of rFVIIa in treatment of nonsurgical, intracranial bleeding in the closed head injury patient. It is known that factor VII levels drop significantly below normal in the first 2 days after head trauma.[3] Therefore, the potential of rFVIIa to limit the progression of bleeding that places increased pressure on the brain may make rFVIIa an ideal treatment for this subset of patients. The authors report here on the use of rFVIIa in 2 noncoagulopathic multitrauma patients with closed head injuries noted to have worsening of intracranial bleeding on follow-up computed tomography (CT).

## PATIENTS AND METHODS

A search of the trauma registry from a level I trauma center identified 2 patients admitted between January 1, 2002 and December 31, 2004 with traumatic, nonsurgical intracranial bleeding who were noted to have progressive hemorrhage on

# Report Documentation Page

*Form Approved*
*OMB No. 0704-0188*

| 1. REPORT DATE **01 SEP 2006** | 2. REPORT TYPE **N/A** | 3. DATES COVERED **-** |
|---|---|---|

| 4. TITLE AND SUBTITLE **Effects of recombinant activated factor VII in traumatic nonsurgical intracranial hemorrhage** | | 5a. CONTRACT NUMBER |
|---|---|---|
| | | 5b. GRANT NUMBER |
| | | 5c. PROGRAM ELEMENT NUMBER |
| 6. AUTHOR(S) **White C. E., Schrank A. E., Baskin T. W., Holcomb J. B.,** | | 5d. PROJECT NUMBER |
| | | 5e. TASK NUMBER |
| | | 5f. WORK UNIT NUMBER |

| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234** | 8. PERFORMING ORGANIZATION REPORT NUMBER |
|---|---|
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | 10. SPONSOR/MONITOR'S ACRONYM(S) |
| | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) |

12. DISTRIBUTION/AVAILABILITY STATEMENT
**Approved for public release, distribution unlimited**

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT **SAR** | 18. NUMBER OF PAGES **8** | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT **unclassified** | b. ABSTRACT **unclassified** | c. THIS PAGE **unclassified** | | | |

**Standard Form 298 (Rev. 8-98)**
Prescribed by ANSI Std Z39-18

follow-up CT and were given rFVIIa as the sole intervention. The CT scans of the head that showed progression of hemorrhage were performed 6 hours after initial head CT as part of an institutional TBI protocol, not as a result of neurological deterioration. The trauma registry was then searched for patients of similar age, sex, and comparable injury severity score (ISS) with progression of initial intracranial bleed identified by CT to serve as a matched sample. No patient was coagulopathic, acidotic, or thrombocytopenic during the first 48 hours after admission, and no blood or blood products were transfused during this time. Intravenous rFVIIa was given as a single dose of 120 mcg/kg, and afterward, those patients were monitored for changes in their neurological examination and evidence of thromboembolic phenomena. Efficacy of the intervention was determined primarily by CT for evidence of hematoma stability or progression as well as by coagulation parameters and neurological examination. Patients A and B received rFVIIa; C and D were their respective controls.

## Patient A

Patient A, a 62-year-old man, fell from a standing height and was brought by ambulance to hospital after losing consciousness. At arrival, his Glasgow Coma Scale (GCS) was 15 with nonfocal neurological examination, and he remained hemodynamically normal. The only significant finding on physical examination was a posterior scalp laceration associated with a cephalohematoma. A CT scan of his head revealed bilateral intraparenchymal hemorrhages as well as a subarachnoid hemorrhage observed in the sulci of the right parietofrontal lobe and perimesencephalic cisterns without mass effect or midline shift (Fig. 1). Repeat head CT following institutional protocol showed significant increase in right frontal parenchymal hematoma with associated edema and gyral effacement (Fig. 2). Neurosurgical evaluation the following morning found the patient to be disoriented, somnolent, and uncooperative with GCS 14 but without focal neurological deficits. Coagulation parameters measured at this time were PT of 14.1, activated partial thromboplastin time (aPTT) of 34.5, INR of 1.1, and platelet count of 202,000. Recombinant activated factor VII was administered as a single dose at 120 mcg/kg with resultant coagulation parameters: PT of 13.3, aPTT of 37.2, and INR of 1.0. Repeat head CT scan at 31 hours showed stable to decreased intraparenchymal and subarachnoid hemorrhages (Fig. 3). Neurological examination at 48 hours post-injury was normal, and he was discharged from hospital with a Glasgow Outcome Scale (GOS) of 5 (good recovery).

## Patient B

Patient B, a 79-year-old woman, was found lying on the floor, minimally responsive after an apparent fall. She was brought to the hospital by ambulance and arrived with a GCS 9. Shortly after presentation, she suffered convulsions and was subsequently intubated for respiratory distress and deteriorating mental status. Physical examination revealed



**FIGURE 1.** Preliminary CT scan, Patient A. Bilateral intraparenchymal hemorrhages and subarachnoid hemorrhage of right parietofrontal lobe and perimesencephalic cisterns.

an occipital hematoma with small posterior scalp laceration and right periorbital ecchymosis, and head CT scan showed right frontal and temporal subdural, subarachnoid, and intraparenchymal hemorrhages without mass effect or herniation (Fig. 4). A linear frontal bone fracture was noted to extend from the sagittal suture to the right orbit. Repeat head CT scan demonstrated a midline shift with new blood in the interpeduncular cistern (Fig. 5). Coagulation parameters and platelet count were PT, 15.5 seconds; aPTT 20.8 seconds; INR 1.1; and PLT 311,000, respectively. A single dose of rFVIIa at 120 mcg/kg was given 6 hours after admission, and a repeat head CT scan performed 4 hours after this intervention demonstrated no increase in midline shift or hemorrhages (Fig. 6). Coagulation parameters after dosing were PT 13.3 seconds; aPTT 26 seconds; and INR 0.9, respectively. A Camino bolt was placed at this time by the neurosurgery service and intracranial pressures (ICP) were normal and remained so throughout the monitored period. Repeat head CT scans showed stable hematomas and no midline shift. The patient continued to improve, and by hospital day 10, her GCS was 15. However, she was noted on neurological examination to have a diffuse left-sided hemiparesis. Her hospital course was complicated by pneumonia followed by *clostridium difficile* colitis. She later died after

**FIGURE 2.** Second CT scan, Patient A. Increased right frontal parenchymal hematoma compared to preliminary CT scan.

cardiopulmonary arrest due to septic complications on HD 29 (GOS: 1).

## Patient C

Patient C was a 63-year-old man who fell from standing height and briefly lost consciousness before emergency medical service (EMS) arrived. On presentation to an outlying facility, the patient became obtunded and was electively intubated. Head CT scan at that time revealed large intraparenchymal and subarachnoid hematomas with midline shift. He was then transferred to the authors' facility where he arrived with a GCS of 10 and an otherwise normal neurological examination. Repeat CT scan of the patient's head showed no change from the previous scan. However, a CT scan performed following the TBI protocol showed progression of right subdural hematoma. Coagulation parameters and platelet count were normal, and neurological examination remained nonfocal. On hospital day 2, the patient became lethargic and would not follow commands. Head CT scan performed 29 hours after injury showed increased left temporal parenchymal and subdural hematomas. His neurological status continued to deteriorate, and a ventriculostomy was placed by the neurosurgery service. This patient proceeded to have a protracted hospital course, which required placement of a Camino bolt after the ventriculostomy became

dislodged and attempted lumbar drain placement. Recovery was also complicated by ventilator-associated pneumonia as well as sacral and occipital decubitus ulcers. He was extubated and discharged to a skilled nursing facility on hospital day 63 with a GOS of 3 (severe disability).

## Patient D

Patient D, a 57-year-old woman, was a backseat passenger involved in a T-bone motor vehicle crash. She was noted to have lost consciousness at the scene and had a GCS of 8 when EMS arrived. She was intubated in the field and presented to the hospital GCS 3T. On physical examination, she had an 8-cm scalp laceration above her left ear and ecchymosis on the right shoulder and chest. Coagulation parameters on arrival were as follows: PT, 14.5 seconds; INR, 1.1; and aPTT, 28 seconds. Head CT scan revealed a left parietal cephalohematoma, diffuse axonal injury, subarachnoid hemorrhage, and intraventricular blood. The TBI protocol head CT scan demonstrated new right frontoparietal subarachnoid hemorrhage, development of left parietal intraparenchymal hemorrhages, and right frontoparietal diffuse axonal injury. No progression was noted on repeat scans. She was extubated but required placement of a percutaneous gastrostomy tube for nutritional support and was discharged to a skilled nursing facility on hospital day 15 with GOS 3 (severe disability).
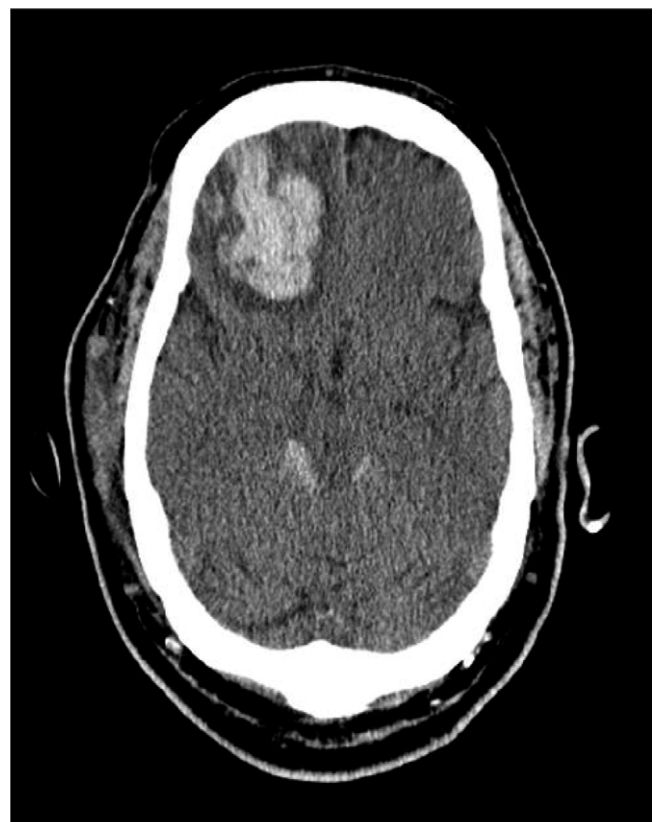


**FIGURE 3.** Third CT scan after single dose of rVIIa Patient A. Decreased intraparenchymal and subarachnoid hemorrhages.

**FIGURE 4.** Preliminary CT scan, Patient B. Right frontal and temporal subdural, subarachnoid, and intraparenchymal hemorrhages.

## DISCUSSION

Traumatic brain injury is the leading cause of death and disability in children and young adults in the United States. It is estimated that each year 1.5 million Americans sustain TBI[4]; 50,000 people die as a result of these injuries, and 80,000 to 90,000 suffer some long-term disability.[4,5] Since the late 1980s, mortality has decreased from 36% to an average of about 15% at specialized TBI centers—a drop that directly correlates with better outcomes in this population. As no new treatments having a positive impact on morbidity or mortality have been introduced to clinical practice during this period,[6] the reason for such improvement is unclear, but it is most likely related to better trauma systems and critical care.

It is well established that blunt brain injury triggers activation of the coagulation system and patients may develop a severe coagulopathy as a result of depletion of these clotting factors.[7-11] In fact, a direct relationship between the severity of coagulopathy and outcome has been confirmed in several studies and probably correlates with the severity of the cerebral destruction.[8] Additionally, clotting time as measured by free oscillatory rheometry at hospital admission has been correlated with GOS as late as 3 months after discharge.[12] Tissue factor, found in capacious quantities in the brain, is released from

damaged cells or expressed on the surface of perturbed endothelial cells and monocytes, or both, and activates the extrinsic pathway resulting in thrombin consumption and fibrin clot.[13] In this milieu, the clot is rapidly cleared and a later diathesis shifting toward hemorrhage rather than microemboli seems to predominate. This result is more pronounced in patients with penetrating injuries (ie, gunshot wounds) as a result of the wider destruction of neural tissue as only 0% to 13% of patients have been shown to be at risk for increased bleeding secondary to coagulation defects from blunt trauma.[11]

The current management strategy of the TBI patient is aimed at preventing secondary insults to an already compromised brain, those injuries that may be interdicted or reversed such as hypoxia and/or hypotension. Within this same precept the focus is on reducing intracranial hypertension, which may permit adequate cerebral perfusion pressure and thereby maintain appropriate levels of oxygen to the brain. Intuitively, reducing the size or halting the progression of an intraparenchymal or subdural hematoma may have some bearing on ICP and ultimate outcome. Initially, severe head injuries can induce a hypercoagulable state, and once coagulation proteins are consumed, a hypocoagulable state may follow that may not be



**FIGURE 5.** Second CT scan, Patient B. Midline shift and new blood in the interpenducular cistern.

**FIGURE 6.** Third CT scan after single dose of rVIIa, Patient B. No increase in the midline shift or hemorrhages demonstrated in Figures 4 and 5.

manifest for up to 3 days.[14] Management of this later coagulopathy centers on fresh frozen plasma (FFP) and cryoprecipitate infusion. Fresh frozen plasma requires time to type and cross-match and thaw and may impose a significant volume burden on a patient already at risk for cerebral edema. Once prepared, FFP must still be infused and may require further dosing for adequate effect, all of which delays interventions such as placement of ICP monitors, ventriculostomies, or surgery.[15] Regarding the rapid onset of coagulopathy in TBI, it has been suggested that for replacement therapy to be effective, it must be started within minutes of injury; however, it is unclear how patients who are to receive such therapy should be identified.[9]

Injury activates the coagulation system through tissue factor/factor VII interaction and leads to the formation of thrombin and fibrin clot. Consequently, if native fibrinolytic processes become overwhelmed, microthrombi appear in the circulation, which may cause organ ischemia with end-organ dysfunction. This process has been implicated in multisystem organ failure (MOF) in lungs, liver, and kidneys and is associated with a high mortality, roughly doubling the risk of death.[16] In TBI, a sudden release or novel exposure to massive amounts of tissue factor precipitates thrombin formation as well as fibrin clot. After this hypercoagulable phase, hemostatic defects begin to occur as a result of consumption of substrate and there is a tendency toward hemorrhage.

Thrombin is a key enzyme in the coagulation cascade. In the last 2 decades, it has become apparent that thrombin has many extravascular effects, from cell survival and proliferation to inflammation, some of which may be deleterious to damaged encephalic tissue.[17,18] Although low concentrations of thrombin may protect the brain from various insults, high concentrations cause brain damage and may increase brain edema as well as kill neurons and astrocytes.[19] There is also a growing body of evidence that thrombin inhibitors ameliorate the neurotoxic effects of thrombin in animal models.[20-22] Additionally, thrombin has been shown to cause vasoconstriction, which can further compromise blood flow to an already damaged brain, recruit inflammatory cells to the site of injury, as well as activate proteinases that may in turn disrupt the blood brain barrier.[23-25]

The exact temporal sequence of the coagulopathy associated with TBI is unknown, but the first phase seems to occur within minutes to 4 hours after injury.[11] This result is probably related to the severity of injury and, thus, the amount of tissue factor exposed to clotting proteins. During this time, there is evidence to suggest that intravascular coagulation is present in cerebral tissue, and this contributes to ischemia and secondary brain injury. Stein et al[26,27] sampled surgical specimens from human cerebral contusions as well as animal models for TBI and found intravascular coagulation even in mild and diffuse injuries although it was more pronounced in focal lesions and more severe trauma. Furthermore, there was a good correlation between density of intravascular microthrombi and neuronal cell necrosis. These findings along with the temporal relation of disseminated intravascular coagulopathy (DIC) have led some to advocate stopping the activation of thrombin early in the course of TBI; however, this would run the risk of bleeding into the injured brain, and so far no prospective study has addressed outcome.[11,13,23] Later therapy is aimed at achieving hemostasis when consumptive coagulopathy is identified, usually with cryoprecipitate or FFP. For the cases presented here, rFVIIa was used for this purpose with effects observed in both coagulation parameters as well as imaging studies.

Delayed traumatic intracerebral hematomas found by CT scan have been noted in more than 7% of all patients with severe cerebral trauma and may be the cause of clinical deterioration in this population.[10] Small hematomas have also been noted to increase in size and may not reach their ultimate size until 12 hours after injury.[28] Van der Sande et al[29] have shown that very high fibrin–fibrinogen degradation products were associated with combined hemorrhagic lesions and mass effect on CT scans, which coincides with the described late coagulopathy. Moreover, failure of nonoperative management has been attributed to the evolution of these preexisting lesions or the development of new ones.[30]

In this group of patients, all were documented by CT scan to have evolution in the size of intracranial lesions, which then abated in the interventional cohort with administration of

**TABLE 1.** Days in Hospital, in ICU, and on Ventilator with Glasgow Outcome Scale

| Patient | Group | Hospital Days | ICU Days | Vent Days | Glasgow Outcome Scale |
|---------|---------|---------------|----------|-----------|------------------------|
| A | Exp | 5 | 3 | 0 | Good Recovery |
| B | Exp | 29 | 29 | 27 | Death |
| C | Control | 63 | 23 | 21 | Severe Disability |
| D | Control | 13 | 6 | 3 | Severe Disability |

rFVIIa with concomitant decrease in PT on coagulation profiles; this has been shown to be a marker of drug efficacy.[31,32] Both rFVIIa patients were beyond a 4-hour window from injury, their coagulations profiles were normal, and neither was transfused FFP before receiving rFVIIa therapy. CT scans were performed for all patients following the TBI protocol, not as a result of clinical deterioration, and no other source of bleeding was identified. Patients in both sets experienced similar hospital, intensive care unit, and ventilator days (Table 1). Of the 2 patients in the interventional set, patient A was discharged from hospital with good neurological function, whereas patient B was noted to have left hemiparesis despite improvement in GCS from 9 to 15 and ability to participate in daily care. Her hospital course was complicated by multiple infections, and she later died of sepsis from pneumonia. Both patients in the convenience sample had poor neurological function at discharge to skilled nursing facilities and were dependent on others for daily support.

Guidelines for nonoperative management of intraparenchymal and subdural hematomas have predominately arisen from experience with spontaneous rather than acute traumatic lesions and are based on hematoma volume as well as its mass effect on intracranial structures.[30] In the hemorrhagic stroke population, where hematoma volume is directly related to outcome, rFVIIa has been shown to limit the growth of the hematoma, reduce mortality, and improve functional outcome.[33] Also, rFVIIa can rapidly lower the INR and appears safe for patients with warfarin-related intracerebral hematomas.[34-36] Although coagulopathy often associated with TBI has not actually proven to be a causative factor of delayed brain injury, halting the progression of a space-occupying lesion in the cranial vault would appear to benefit this population as well. In addition, rapid correction of coagulation disorders with rFVIIa might allow for timely placement of ICP monitors or ventriculostomies and therefore more aggressive care of these critically ill patients. The timing of rFVIIa therapy in TBI, however, remains to be defined as there is theoretically a higher risk of cerebral thrombosis early in the course of injury, although this more than likely dissipates as clotting factors are depleted. Actually restoring physiologic titers of thrombin into damaged cerebral tissue may have some protective effect.

Recombinant activated factor VII concentrate is a synthetic activated clotting factor that enhances localized clot formation at the site of endothelial injury.[37] When administered at pharmacological doses, it circulates at concentrations 1000 times higher than normal.[1] Its half-life is approximately 2.3 hours, which is much longer than that of other activated clotting factors.[37] High plasma levels of rFVIIa lead to faster and higher localized thrombin production and *in vitro* analyses of clots produced in a thrombin-rich environment have demonstrated resistance to fibrinolysis.[38]

This mechanism of action of rFVIIa has raised concerns about its potential to induce systemic thrombotic events. However, after more than 750,000 doses, the reported rate of serious adverse events remains less than 1%.[1,2] Serious complications reported in the literature include acute myocardial infarction, angina, acute renal failure, cerebrovascular accident leading to hemiparesis, deep venous thrombosis, fatal pulmonary embolism, and DIC.[39] Complications typically occurred days to weeks after treatment in patients with underlying disease that predisposed them to development of thrombosis. Of note, Mayer et al[33] reported a higher incidence of thromboembolic events when treating spontaneous intracerebral hemorrhage with rFVIIa and O'Connell et al[40] reported that most adverse events followed the use of rFVIIa for unlabled indications, although this latter study represents a self-reported registry. In this series, patient B was noted to have a residual left hemiparesis that may have been the result of drug administration. As this is currently an off-label use of rFVIIa, potential risks and benefits must be carefully weighed before drug use. Recombinant activated factor VII cannot be recommended in patients in hypercoagulable states, such as sepsis or perhaps early in head trauma, but this subject awaits evaluation in future clinical trials.

Currently, rFVIIa is indicated for the treatment of spontaneous and surgical bleeding in congenital hemophilia A and B patients with inhibitors to factors VIII and IX, and it is approved in Europe for the treatment of patients with acquired hemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia. The literature now contains initial clinical trials as well as many case reports indicating its usefulness in treating life-threatening hemorrhage. However, there is little data regarding the treatment of TBI with rFVIIa outside of a case series with few subjects. There is interest in patients with spontaneous intracerebral hemorrhage as well as with non-trauma neurosurgical patients, but the results may not extrapolate to TBI population as a result of the intense coagulopathy associated with head trauma.[8] This series is small, was drawn retrospectively from the trauma registry, and therefore has the inherent flaws associated with this type of study. The criteria for selection of the intervention cohort included patients with progressive nonsurgical intracranial bleeding who had not received other clotting factors before administration of rFVIIa; a

matched convenience sample was drawn from the same pool in the interest of comparison.

Recombinant activated factor VII has the potential to limit or even halt the progression of bleeding in hemorrhagic TBI that would otherwise place growing pressure on the brain. As such, these data suggest that the use of rFVIIa holds promise in the setting of nonsurgical intracranial bleeding. Whether this usage will have a positive impact on neurological outcome lies in a future prospective clinical trial whose planning is underway.

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